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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/520,901	04/13/2005	Toshiyoshi Fujiwara	09857/0202272-US0	2780

7278 7590 01/20/2010

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EXAMINER	
SHEN, WU CHENG WINSTON	
ART UNIT	PAPER NUMBER
1632	

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01/20/2010	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/520,901	FUJIWARA ET AL.	
	Examiner	Art Unit	
	WU-CHENG Winston SHEN	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *04 November 2009*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *4-21* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *4-21* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *07 January 2005* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Applicant's claim amendments filed on 11/04/2009 have been entered. The Declaration by Toshiyoshi Fujiwara filed on 11/04/2009 has been considered.

Claims 1-3 are cancelled. Claims 4 and 8 are amended. Claims 13-21 are newly added. Claims 4-21 are pending and currently under examination.

This application 10/520,501 is a 371 of PCT/JP03/08573 filed on 07/07/2003, and claims the benefits of foreign application JAPAN 2002-198941 07/08/2002.

Claim objections

1. Claims 13-16 and 21 are objected to under 37 CFR 1.75 as being a substantial duplicate of claims 4-7 and 12 respectively. When two claims in an application are duplicates or else are so close in content that they both cover the same thing, despite a slight difference in wording, it is proper after allowing one claim to object to the other as being a substantial duplicate of the allowed claim. See MPEP § 706.03(k).

Amended claim 4 filed on 11/04/2009 reads as follows: A polynucleotide cassette comprising an hTERT promoter operably linked with an E1A gene, an IRES sequence, and an E1B gene in this order, wherein the cassette is capable of replicating in a local cancer area, and wherein the hTERT promoter consists of the nucleotide sequence of SEQ ID NO: 4, the E1A gene consists of the nucleotide sequence of SEQ ID NO: 1, the IRES sequence consists of the nucleotide sequence of SEQ ID NO: 3, and the E1B gene consists of the nucleotide sequence of SEQ ID NO: 2.

Newly added claim 13 filed on 11/04/2009 reads as follows: A polynucleotide cassette comprising an hTERT promoter operably linked with an E1A gene, an IRES sequence, and an E1B gene in this order, wherein the cassette is capable of replicating in a cancer cell, and

wherein the hTERT promoter consists of the nucleotide sequence of SEQ ID NO: 4, the E1A gene consists of the nucleotide sequence of SEQ ID NO: 1, the IRES sequence consists of the nucleotide sequence of SEQ ID NO: 3, and the E1B gene consists of the nucleotide sequence of SEQ ID NO: 2.

It is noted that "capable of replicating in a local cancer area" recited in claim 4 and "capable of replicating in a cancer cell" recited in claim 13 are inherent characteristics of the recited "polynucleotide cassette" and these limitations do not impart any structural difference of the "polynucleotide cassette" recited in claim 4 versus the "polynucleotide cassette" recited in claim 13.

Claim Rejection - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

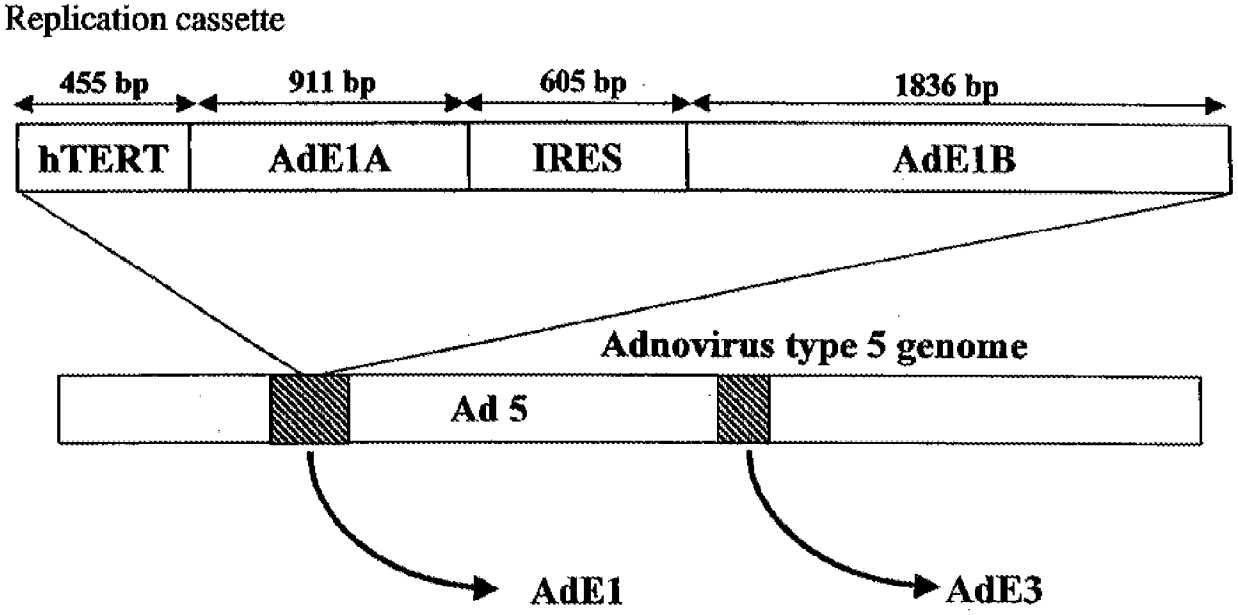
> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter, which the applicant regards as his invention.

2. Claims 4-21 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. *This rejection is necessitated by claim amendments filed on 11/04/2009.*

Amended claim 4 and newly added claim 13 recite the limitation "wherein the hTERT promoter consists of the nucleotide sequence of SEQ ID NO: 4, the E1A gene consists of the nucleotide sequence of SEQ ID NO: 1, the IRES sequence consists of the nucleotide sequence of SEQ ID NO: 3, and the E1B gene consists of the nucleotide sequence of SEQ ID NO: 2".

In the reply filed on 11/04/2009, Applicant states that "Support for these claims is found throughout the specification. For example, support for claim 13, is found in Figure 1, page 2, paragraphs [0020] - [0029]. Support for claims 14-16, is found, for example, page 2, paragraph [0037] through to page 3, paragraphs [0038]-[0043]. Support for claims 17-21, are found for example, page 3, paragraphs [0039]-[0049]".

The specification discloses that SEQ ID No: 1 (i.e. E1A) is an 899-nucleotide long polynucleotides; SEQ ID No: 2 (i.e. E1B) is an 1823-nucleotide long polynucleotide; SEQ ID No: 3 (i.e. IRES) is a 605-nucleotide long polynucleotide; and SEQ ID No: 4 (i.e. hTERT) is a 455-nucleotide polynucleotide. Figure 1 disclosed in the specification is shown below.



It is noted that (i) the AdE1A discloses in Figure 1 is 911 base-pair (bp) whereas SEQ ID No: 1 (i.e. E1A) disclosed in the specification is 899-nucleotide long polynucleotides; and (ii) the AdE1B discloses in Figure 1 is 1836 base-pair (bp) whereas SEQ ID No: 2 (i.e. E1B) is an 1823-nucleotide long polynucleotide. It is noted that "consists of" recited in claims 1 and 13 is a close language, which indicates E1A is exactly the sequences of SEQ ID No: 1 and E1B is exactly the

sequences of SEQ ID No: 2. The discrepancy in the length of SEQ ID No: 1 and the length of AdE1A shown in Figure1, and the discrepancy in the length of SEQ ID No: 2 and the length of AdE1B shown in Figure 1 render claims 4 and 13 unclear regarding exactly what nucleotide sequences are included in the E1A and E1B recited in claims 4 and 13 of claimed polynucleotide cassette.

As a related issue, Applicant is advised to clarify on the record the relationship, at nucleotide level, between the following seemly closely related, perhaps identical, viral vectors: (i) the infectious recombinant adenovirus (TRAD) disclosed in Example 1 of specification (ii) viral vector construct "OBP-301" cited on page 2 of the Declaration filed by Toshiyoshi Fujiwara filed on 11/04/2009, (iii) "Telomelysin" cited on page 3 of the Declaration filed by Toshiyoshi Fujiwara filed on 11/04/2009, and (iv) claims 6 and 15 filed on 11/04/2009.

Claims 5-12 depend from claim 4, and claims 14-21 depend from claim 13.

Claim Rejection - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

3. Previous rejection of claims 4-8, 11, and 12 under 35 U.S.C. 103(a) as being unpatentable over **Morin et al.** (Morin et al., 2000, WO 00/46355, international publication date, August 10, 2000; this reference is disclosed in IDS filed on 04/25/2006, listed as reference No. BA) in view

of **Li et al.** (Li et al., A hepatocellular carcinoma-specific adenovirus variant, CV890, eliminates distant human liver tumors in combination with doxorubicin. *Cancer Res.* 61(17): 6428-36, 2001; this reference is disclosed in IDS filed on 04/25/2006, listed as reference CC), is ***withdrawn*** because the claims have been amended.

Amended claim 4 filed on 11/04/2009 reads as follows: A polynucleotide cassette comprising an hTERT promoter operably linked with an E1A gene, an IRES sequence, and an E1B gene in this order, wherein the cassette is capable of replicating in a local cancer area, and wherein the hTERT promoter consists of the nucleotide sequence of SEQ ID NO: 4, the E1A gene consists of the nucleotide sequence of SEQ ID NO: 1, the IRES sequence consists of the nucleotide sequence of SEQ ID NO: 3, and the E1B gene consists of the nucleotide sequence of SEQ ID NO: 2.

Neither Morin et al. nor Li et al. teaches the newly added limitation "wherein the hTERT promoter consists of the nucleotide sequence of SEQ ID NO: 4, the E1A gene consists of the nucleotide sequence of SEQ ID NO: 1, the IRES sequence consists of the nucleotide sequence of SEQ ID NO: 3, and the E1B gene consists of the nucleotide sequence of SEQ ID NO: 2".

4. Previous rejection of claims 4, 5, 8, 9, and 10 under 35 U.S.C. 103(a) as being unpatentable over **Morin et al.** (Morin et al., 2000, WO 00/46355, international publication date, August 10, 2000; this reference is disclosed in IDS filed on 04/25/2006, listed as reference No. BA) in view of **Li et al.** (Li et al., A hepatocellular carcinoma-specific adenovirus variant, CV890, eliminates distant human liver tumors in combination with doxorubicin. *Cancer Res.* 61(17): 6428-36, 2001; this reference is disclosed in IDS filed on 04/25/2006, listed as reference CC) as applied to claims 4-8, 11 and 12 above, and further in view of **Cheng et al.** (Cheng et al., U.S. patent application No. 2003/0104625, publication date, June 5, 2003; filed Feb. 22, 2002;

this reference is cited in the office action dated 06/19/2007) is ***withdrawn*** because the claims have been amended.

Amended claim 4 filed on 11/04/2009 reads as follows: A polynucleotide cassette comprising an hTERT promoter operably linked with an E1A gene, an IRES sequence, and an E1B gene in this order, wherein the cassette is capable of replicating in a local cancer area, and wherein the hTERT promoter consists of the nucleotide sequence of SEQ ID NO: 4, the E1A gene consists of the nucleotide sequence of SEQ ID NO: 1, the IRES sequence consists of the nucleotide sequence of SEQ ID NO: 3, and the E1B gene consists of the nucleotide sequence of SEQ ID NO: 2.

None of Morin et al., Li et al., and Cheng teaches the newly added limitation "wherein the hTERT promoter consists of the nucleotide sequence of SEQ ID NO: 4, the E1A gene consists of the nucleotide sequence of SEQ ID NO: 1, the IRES sequence consists of the nucleotide sequence of SEQ ID NO: 3, and the E1B gene consists of the nucleotide sequence of SEQ ID NO: 2".

5. Previous rejection of claims 4-12 are rejected under 35 U.S.C. 103(a) as being unpatentable over **Morin et al.** (Morin et al., 2000, WO 00/46355, international publication date, August 10, 2000; this reference is disclosed in IDS filed on 04/25/2006, listed as reference No. BA) in view of **Yu et al.** (US 6,692,736, issued on 02/17/2004, filed on 03/21/2001), is ***withdrawn*** because the claims have been amended.

Amended claim 4 filed on 11/04/2009 reads as follows: A polynucleotide cassette comprising an hTERT promoter operably linked with an E1A gene, an IRES sequence, and an E1B gene in this order, wherein the cassette is capable of replicating in a local cancer area, and wherein the hTERT promoter consists of the nucleotide sequence of SEQ ID NO: 4, the E1A

gene consists of the nucleotide sequence of SEQ ID NO: 1, the IRES sequence consists of the nucleotide sequence of SEQ ID NO: 3, and the E1B gene consists of the nucleotide sequence of SEQ ID NO: 2.

Neither Morin et al. nor Yu et al., and Cheng teaches the newly added limitation "wherein the hTERT promoter consists of the nucleotide sequence of SEQ ID NO: 4, the E1A gene consists of the nucleotide sequence of SEQ ID NO: 1, the IRES sequence consists of the nucleotide sequence of SEQ ID NO: 3, and the E1B gene consists of the nucleotide sequence of SEQ ID NO: 2".

The following 103 rejections are necessitated by claim amendments filed on 11/04/2009. It is noted that Applicant's arguments regarding newly added limitation reciting SEQ ID numbers 1-4 in amended claims 4 and 13 are addressed as the related to the new grounds of rejections set forth below.

6. Claims 4-8, 11-17, 20, and 21 are rejected under 35 U.S.C. 103(a) as being unpatentable over **Morin et al.** (Morin et al., 2000, WO 00/46355, international publication date, August 10, 2000; this reference is disclosed in IDS filed on 04/25/2006, listed as reference No. BA) in view of **Li et al.** (Li et al., A hepatocellular carcinoma-specific adenovirus variant, CV890, eliminates distant human liver tumors in combination with doxorubicin. *Cancer Res.* 61(17): 6428-36, 2001; this reference is disclosed in IDS filed on 04/25/2006, listed as reference CC), **Stuart et al.** (WO 2002/20754, international publication date 03/14/2002), **Nemerow et al.** (WO 2000/42208, international publication date 07/20/2000), **Arya** (WO 2000/40741, international

publication date 07/13/2000), and **Hagen et al.** (WO 1999/33998, international publication date 07/08/1999). *This rejection is necessitated by claim amendments filed on 11/04/2009.*

It is noted that Stuart et al. (WO 2002/20754, 686 pages), Nemerow et al. (WO 2000/42208, 212 pages), Arya (WO 2000/40741, 144 pages), and Hagen et al. (WO 1999/33998, 100 pages) are relied on, respectively, for the disclosure of SEQ D No: 1, SEQ D No: 2, SEQ ID No: 3, and SEQ ID No: 4 of instant application. Only cover pages from each of these four references are included along with this office action. The sequence alignments are provided below in this office action.

Amended claim 4 filed on 11/04/2009 reads as follows: A polynucleotide cassette comprising an hTERT promoter operably linked with an E1A gene, an IRES sequence, and an E1B gene in this order, wherein the cassette is capable of replicating in a local cancer area, and wherein the hTERT promoter consists of the nucleotide sequence of SEQ ID NO: 4, the E1A gene consists of the nucleotide sequence of SEQ ID NO: 1, the IRES sequence consists of the nucleotide sequence of SEQ ID NO: 3, and the E1B gene consists of the nucleotide sequence of SEQ ID NO: 2.

Amended claim 8 filed on 11/04/2009 reads as follows: A method of killing cancer cells, comprising the step of: locally administering an effective amount of the recombinant virus according to claim 5 to a patient in need thereof, such that the recombinant virus is capable of replicating in a local cancer area of the patient, and wherein replication of the recombinant virus kills the cancer cell in the local cancer area.

Newly added claim 13 filed on 11/04/2009 reads as follows: A polynucleotide cassette comprising an hTERT promoter operably linked with an E1A gene, an IRES sequence, and an E1B gene in this order, wherein the cassette is capable of replicating in a cancer cell, and wherein the hTERT promoter consists of the nucleotide sequence ofSEQ ID NO: 4, the E1A gene consists of the nucleotide sequence of SEQ ID NO: 1, the IRES sequence consists of the

nucleotide sequence of SEQ ID NO: 3, and the E1B gene consists of the nucleotide sequence of SEQ ID NO: 2.

Newly added claim 17 filed on 11/04/2009 reads as follows: A method of killing cancer cells, comprising the step of: administering an effective amount of the recombinant virus according to claim 14 to a patient in need thereof, such that the recombinant virus is capable of replicating in a cancer cell of the patient, and wherein replication of the recombinant virus kills the cancer cell.

Morin et al. (2000) discloses use of the hTERT promoter to selectively direct expression in cancer cells. More specifically, Morin et al., 2000 teaches oncolytic viruses, in which a toxin or a genetic element essential for viral replication is placed under control of the TERT promoter. Thereby, the virus that replicates preferentially in cells expressing TERT, and thereby selectively lyses cancer cells (See *in vitro* Example 4 on transfected human cell lines, pages 35-36, and *in situ* Example 3 on transplanted human tumor 143B cells on nude mice, page 35, Morin et al., 2000).

While Morin et al. does not teach an adenovirus with IRES inserted between E1A and E1B in an adenovirus, as recited in claims 4 and 13 of instant application, operably linked to the hTERT promoter, **Li et al.** teaches an adenoviral construct comprising promoter AFP (α-Fetoprotein, a hepatocyte specific promoter) operably linked to **E1A-IRES-E1B** to cause efficient replication and destruction of human hepatocarcinoma cells transplanted on a mouse. Furthermore, Li et al. teaches intratumoral injection [which reads on "locally administering an effective amount of the recombinant virus" in "a local cancer area" recited in claim 8 and "administering an effective amount of the recombinant virus" recited in newly added claim 17 filed on 11/04/2009] of the adenoviral construct (See line 4, left column of page 6430, Li et al.).

While Morin et al. do not teach "wherein the hTERT promoter consists of the nucleotide sequence of SEQ ID NO: 4, the E1A gene consists of the nucleotide sequence of SEQ ID NO: 1, the IRES sequence consists of the nucleotide sequence of SEQ ID NO: 3, and the E1B gene consists of the nucleotide sequence of SEQ ID NO: 2" recited in claims 4 and 13, **Stuart et al.** (WO 2002/20754) teaches sequences that matches 100% to SEQ ID NO:1 of instant application, **Nemerow** (WO 2000/42208) teaches sequences that match 100% to SEQ ID No:2 of instant application, **Arya** (WO 2000/40741) teaches sequences that match 100% to SEQ ID No:3 of instant application, and **Hagen et al.** (WO 1999/33998) teaches sequences that match 100% to SEQ ID No: 4 of instant application. The sequence alignments of SEQ ID No: 1-4 of instant applcaition to the sequences disclosed in the respective prior arts are provided below.

SEQ ID No: 1 (E1A gene)

```
RESULT 8
ABK71579
ID   ABK71579 standard; cDNA; 1247 BP.
XX
AC   ABK71579;
XX
DT   30-JUL-2002  (first entry)
XX
DE   Human dithp polynucleotide #45.
XX
KW   Human; dithp; diagnostic and therapeutic polynucleotide; gene; ss; bone;
KW   cell proliferative disorder; cancer; tumour; autoimmune disorder; brain;
KW   inflammatory disorder; viral infection; bacterial infection; seizure;
KW   fungal infection; parasitic infections; developmental disorder; breast;
KW   endocrine disorder; metabolic disorder; neurological disorder; cervix;
KW   gastrointestinal disorder; transport disorder; gene therapy; kidney;
KW   adrenal gland; bone marrow; lung; ovary; pancreas; prostate; spleen;
KW   skin; testis; thymus.
XX
OS   Homo sapiens.
XX
PN   WO200220754-A2.
XX
PD   14-MAR-2002.
XX
PF   29-AUG-2001; 2001WO-US027127.
XX
PR   05-SEP-2000; 2000US-0229747P.
PR   05-SEP-2000; 2000US-0229748P.
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PR 05-SEP-2000; 2000US-0229749P.
PR 05-SEP-2000; 2000US-0229750P.
PR 05-SEP-2000; 2000US-0229751P.
PR 05-SEP-2000; 2000US-0230583P.
PR 06-SEP-2000; 2000US-0230505P.
PR 06-SEP-2000; 2000US-0230514P.
PR 06-SEP-2000; 2000US-0230515P.
PR 06-SEP-2000; 2000US-0230517P.
PR 06-SEP-2000; 2000US-0230518P.
PR 06-SEP-2000; 2000US-0230519P.
PR 06-SEP-2000; 2000US-0230595P.
PR 06-SEP-2000; 2000US-0230597P.
PR 06-SEP-2000; 2000US-0230598P.
PR 06-SEP-2000; 2000US-0230599P.
PR 06-SEP-2000; 2000US-0230610P.
PR 06-SEP-2000; 2000US-0230865P.
PR 06-SEP-2000; 2000US-0230988P.
PR 07-SEP-2000; 2000US-0230951P.
PR 07-SEP-2000; 2000US-0231163P.
PR 07-SEP-2000; 2000US-0231167P.
XX
PA (INCY-) INCYTE GENOMICS INC.
XX
PI Stuart J, Lincoln SE, Altus CM, Dufour GE, Chalup MS, Hillman JL;
PI Jones AL, Yu JY, Wright RJ, Gietzen D, Liu TF, Yap PE, Dahl CR;
PI Momiyama MG, Bradley DL, Rohatgi SD, Harris B, Roseberry AM;
PI Gerstin EH, Peralta CH, David MH, Panzer SR, Flores V, Daffo A;
PI Marwaha R, Chen AJ, Chang SC, Au AP, Inman RR;
XX
DR WPI; 2002-383054/41.
DR P-PSDB; ABG59987.
XX
PT An isolated polynucleotide useful in diagnostics and therapeutics.
XX
PS Claim 1; Page 427-428; 686pp; English.
XX
CC The invention relates to human diagnostic and therapeutic (dithp)
CC polynucleotides and their associated polypeptides (DITHP polypeptides).
CC The sequences of the invention are used in the treatment and diagnosis of
CC cell proliferative disorders (e.g. atherosclerosis, cirrhosis), cancers
CC (e.g. tumours of the adrenal gland, bone, bone marrow, brain, breast,
CC cervix, kidney, lung, ovary, pancreas, prostate, skin, spleen, testis or
CC thymus), autoimmune/inflammatory disorders (e.g. asthma, bronchitis,
CC psoriasis, osteoporosis), viral infections, bacterial infections, fungal
CC infections, parasitic infections, developmental disorders (e.g. anaemia,
CC epilepsy), seizure disorders (e.g. cerebral palsy, spina bifida),
CC endocrine disorders (e.g. thrombosis, aneurysm), metabolic disorders
CC (e.g. obesity, diabetes), neurological disorders (e.g. stroke,
CC amyotrophic lateral sclerosis, multiple sclerosis), gastrointestinal
CC disorders (e.g. ulcerative colitis, lysinuria) and transport disorders
CC (e.g. myotonic dystrophy, catatonia, peripheral neuropathy). Sequences
CC ABK71535-ABK71809 represent human dithp polynucleotides of the invention
XX
SQ Sequence 1247 BP; 270 A; 308 C; 344 G; 325 T; 0 U; 0 Other;

Query Match 100.0%; Score 899; DB 1; Length 1247;
Best Local Similarity 100.0%;
Matches 899; Conservative 0; Mismatches 0; Indels 0; Gaps 0;

Qy 1 ACACCGGGACTGAAAATGAGACATATTATCTGCCACGGAGGTGTTATTACCGAAGAAATG 60

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                ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        282 ACACCGGGACTGAAAATGAGACATATTATCTGCCACGGAGGTGTTATTACCGAAGAAATG 341

Qy         61 GCCGCCAGTCTTTTGGACCAGCTGATCGAAGAGGTACTGGCTGATAATCTTCCACCTCCT 120
                ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        342 GCCGCCAGTCTTTTGGACCAGCTGATCGAAGAGGTACTGGCTGATAATCTTCCACCTCCT 401

Qy        121 AGCCATTTTGAACCACCTACCCTTCACGAACTGTATGATTTAGACGTGACGGCCCCCGAA 180
                ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        402 AGCCATTTTGAACCACCTACCCTTCACGAACTGTATGATTTAGACGTGACGGCCCCCGAA 461

Qy        181 GATCCCAACGAGGAGGCGGTTTCGCAGATTTTTCCCGACTCTGTAATGTTGGCGGTGCAG 240
                ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        462 GATCCCAACGAGGAGGCGGTTTCGCAGATTTTTCCCGACTCTGTAATGTTGGCGGTGCAG 521

Qy        241 GAAGGGATTGACTTACTCACTTTTCCGCCGGCGCCCGGTTCTCCGGAGCCGCCTCACCTT 300
                ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        522 GAAGGGATTGACTTACTCACTTTTCCGCCGGCGCCCGGTTCTCCGGAGCCGCCTCACCTT 581

Qy        301 TCCCGGCAGCCCGAGCAGCCGGAGCAGAGAGCCTTGGGTCCGGTTTCTATGCCAAACCTT 360
                ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        582 TCCCGGCAGCCCGAGCAGCCGGAGCAGAGAGCCTTGGGTCCGGTTTCTATGCCAAACCTT 641

Qy        361 GTACCGGAGGTGATCGATCTTACCTGCCACGAGGCTGGCTTTCCACCCAGTGACGACGAG 420
                ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        642 GTACCGGAGGTGATCGATCTTACCTGCCACGAGGCTGGCTTTCCACCCAGTGACGACGAG 701

Qy        421 GATGAAGAGGGTGAGGAGTTTGTGTTAGATTATGTGGAGCACCCCGGGCACGGTTGCAGG 480
                ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        702 GATGAAGAGGGTGAGGAGTTTGTGTTAGATTATGTGGAGCACCCCGGGCACGGTTGCAGG 761

Qy        481 TCTTGTCATTATCACCGGAGGAATACGGGGGACCCAGATATTATGTGTTCGCTTTGCTAT 540
                ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        762 TCTTGTCATTATCACCGGAGGAATACGGGGGACCCAGATATTATGTGTTCGCTTTGCTAT 821

Qy        541 ATGAGGACCTGTGGCATGTTTGTCTACAGTCCTGTGTCTGAACCTGAGCCTGAGCCCGAG 600
                ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        822 ATGAGGACCTGTGGCATGTTTGTCTACAGTCCTGTGTCTGAACCTGAGCCTGAGCCCGAG 881

Qy        601 CCAGAACCGGAGCCTGCAAGACCTACCCGCCGTCCTAAAATGGCGCCTGCTATCCTGAGA 660
                ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        882 CCAGAACCGGAGCCTGCAAGACCTACCCGCCGTCCTAAAATGGCGCCTGCTATCCTGAGA 941

Qy        661 CGCCCGACATCACCTGTGTCTAGAGAATGCAATAGTAGTACGGATAGCTGTGACTCCGGT 720
                ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        942 CGCCCGACATCACCTGTGTCTAGAGAATGCAATAGTAGTACGGATAGCTGTGACTCCGGT 1001

Qy        721 CCTTCTAACACACCTCCTGAGATACACCCGGTGGTCCCGCTGTGCCCCATTAAACCAGTT 780
                ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db       1002 CCTTCTAACACACCTCCTGAGATACACCCGGTGGTCCCGCTGTGCCCCATTAAACCAGTT 1061

Qy        781 GCCGTGAGAGTTGGTGGGCGTCGCCAGGCTGTGGAATGTATCGAGGACTTGCTTAACGAG 840
                ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db       1062 GCCGTGAGAGTTGGTGGGCGTCGCCAGGCTGTGGAATGTATCGAGGACTTGCTTAACGAG 1121

Qy        841 CCTGGGCAACCTTTGGACTTGAGCTGTAAACGCCCCAGGCCATAAGGTGTAAACCTGTG 899
                ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db       1122 CCTGGGCAACCTTTGGACTTGAGCTGTAAACGCCCCAGGCCATAAGGTGTAAACCTGTG 1180
```

SEQ ID NO: 2 (E1B gene)

```
RESULT 15
AAA59076
ID   AAA59076 standard; DNA; 7607 BP.
XX
AC   AAA59076;
XX
DT   07-NOV-2000  (first entry)
XX
DE   Nucleotide sequence of plasmid GRE5-E1-SV40-Hygro.
XX
KW   Adenovirus; tripartite leader; adenovirus vector particle; gene delivery;
KW   ss.
XX
OS   Synthetic.
XX
PN   WO200042208-A1.
XX
PD   20-JUL-2000.
XX
PF   14-JAN-2000; 2000WO-EP000265.
XX
PR   14-JAN-1999;   99US-0115920P.
XX
PA   (NOVS ) NOVARTIS AG.
PA   (NOVS ) NOVARTIS-ERFINDUNGEN VERW GES MBH.
PA   (SCRI ) SCRIPPS RES INST.
XX
PI   Nemerow GR,  Von Seggern DJ,  Hallenbeck PL,  Stevenson SC;
PI   Skripchenko Y;
XX
DR   WPI; 2000-476068/41.
XX
PT   New nucleic acid comprising an adenovirus tripartite leader nucleotide
PT   for producing high-capacity and targeted vectors for adenovirus-based
PT   gene therapy.
XX
PS   Example 6; Page 190-192; 212pp; English.
XX
CC   The specification describes a nucleic acid molecule comprising an
CC   adenovirus (AV) tripartite leader (TPL) nucleotide with a sequence
CC   comprising two different TPL exons or three same or different TPL exons.
CC   The nucleic acid is used to produce an adenovirus vector particle,
CC   deliver an exogenous gene to a target cell, pseudotype recombinant viral
CC   vectors, target an adenovirus vector to a cell, produce a modified
CC   adenovirus, deliver a heterologous gene to an animal and produce a
CC   gutless adenoviral vector particle. The present sequence represents
CC   plasmid GRE5-E1-SV40-Hygro, which is used in the course of the invention
XX
SQ   Sequence 7607 BP; 1838 A; 1733 C; 2001 G; 2035 T; 0 U; 0 Other;

  Query Match             100.0%;  Score 1823;  DB 1;  Length 7607;
  Best Local Similarity   100.0%;
  Matches 1823;  Conservative    0;  Mismatches    0;  Indels    0;  Gaps    0;

Qy          1 CTGACCTCATGGAGGCTTGGGAGTGTTTGGAAGATTTTTCTGCTGTGCGTAACTTGCTGG 60
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db       2123 CTGACCTCATGGAGGCTTGGGAGTGTTTGGAAGATTTTTCTGCTGTGCGTAACTTGCTGG 2182
```

```
Qy         61 AACAGAGCTCTAACAGTACCTCTTGGTTTTGGAGGTTTCTGTGGGGCTCATCCCAGGCAA 120
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db       2183 AACAGAGCTCTAACAGTACCTCTTGGTTTTGGAGGTTTCTGTGGGGCTCATCCCAGGCAA 2242

Qy        121 AGTTAGTCTGCAGAATTAAGGAGGATTACAAGTGGGAATTTGAAGAGCTTTTGAAATCCT 180
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db       2243 AGTTAGTCTGCAGAATTAAGGAGGATTACAAGTGGGAATTTGAAGAGCTTTTGAAATCCT 2302

Qy        181 GTGGTGAGCTGTTTGATTCTTTGAATCTGGGTCACCAGGCGCTTTTCCAAGAGAAGGTCA 240
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db       2303 GTGGTGAGCTGTTTGATTCTTTGAATCTGGGTCACCAGGCGCTTTTCCAAGAGAAGGTCA 2362

Qy        241 TCAAGACTTTGGATTTTTCCACACCGGGGCGCGCTGCGGCTGCTGTTGCTTTTTTGAGTT 300
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db       2363 TCAAGACTTTGGATTTTTCCACACCGGGGCGCGCTGCGGCTGCTGTTGCTTTTTTGAGTT 2422

Qy        301 TTATAAAGGATAAATGGAGCGAAGAAACCCATCTGAGCGGGGGGTACCTGCTGGATTTTC 360
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db       2423 TTATAAAGGATAAATGGAGCGAAGAAACCCATCTGAGCGGGGGGTACCTGCTGGATTTTC 2482

Qy        361 TGGCCATGCATCTGTGGAGAGCGGTTGTGAGACACAAGAATCGCCTGCTACTGTTGTCTT 420
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db       2483 TGGCCATGCATCTGTGGAGAGCGGTTGTGAGACACAAGAATCGCCTGCTACTGTTGTCTT 2542

Qy        421 CCGTCCGCCCGGCGATAATACCGACGGAGGAGCAGCAGCAGCAGCAGGAGGAAGCCAGGC 480
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db       2543 CCGTCCGCCCGGCGATAATACCGACGGAGGAGCAGCAGCAGCAGCAGGAGGAAGCCAGGC 2602

Qy        481 GGCGGCGGCAGGAGCAGAGCCCATGGAACCCGAGAGCCGGCCTGGACCCTCGGGAATGAA 540
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db       2603 GGCGGCGGCAGGAGCAGAGCCCATGGAACCCGAGAGCCGGCCTGGACCCTCGGGAATGAA 2662

Qy        541 TGTTGTACAGGTGGCTGAACTGTATCCAGAACTGAGACGCATTTTGACAATTACAGAGGA 600
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db       2663 TGTTGTACAGGTGGCTGAACTGTATCCAGAACTGAGACGCATTTTGACAATTACAGAGGA 2722

Qy        601 TGGGCAGGGGCTAAAGGGGGTAAAGAGGGAGCGGGGGGCTTGTGAGGCTACAGAGGAGGC 660
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db       2723 TGGGCAGGGGCTAAAGGGGGTAAAGAGGGAGCGGGGGGCTTGTGAGGCTACAGAGGAGGC 2782

Qy        661 TAGGAATCTAGCTTTTAGCTTAATGACCAGACACCGTCCTGAGTGTATTACTTTTCAACA 720
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db       2783 TAGGAATCTAGCTTTTAGCTTAATGACCAGACACCGTCCTGAGTGTATTACTTTTCAACA 2842

Qy        721 GATCAAGGATAATTGCGCTAATGAGCTTGATCTGCTGGCGCAGAAGTATTCCATAGAGCA 780
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db       2843 GATCAAGGATAATTGCGCTAATGAGCTTGATCTGCTGGCGCAGAAGTATTCCATAGAGCA 2902

Qy        781 GCTGACCACTTACTGGCTGCAGCCAGGGGATGATTTTGAGGAGGCTATTAGGGTATATGC 840
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db       2903 GCTGACCACTTACTGGCTGCAGCCAGGGGATGATTTTGAGGAGGCTATTAGGGTATATGC 2962

Qy        841 AAAGGTGGCACTTAGGCCAGATTGCAAGTACAAGATCAGCAAACTTGTAAATATCAGGAA 900
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db       2963 AAAGGTGGCACTTAGGCCAGATTGCAAGTACAAGATCAGCAAACTTGTAAATATCAGGAA 3022

Qy        901 TTGTTGCTACATTTCTGGGAACGGGGCCGAGGTGGAGATAGATACGGAGGATAGGGTGGC 960
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db       3023 TTGTTGCTACATTTCTGGGAACGGGGCCGAGGTGGAGATAGATACGGAGGATAGGGTGGC 3082
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Qy        961 CTTTAGATGTAGCATGATAAATATGTGGCCGGGGGTGCTTGGCATGGACGGGGTGGTTAT 1020
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db       3083 CTTTAGATGTAGCATGATAAATATGTGGCCGGGGGTGCTTGGCATGGACGGGGTGGTTAT 3142

Qy       1021 TATGAATGTAAGGTTTACTGGCCCCAATTTTAGCGGTACGGTTTTCCTGGCCAATACCAA 1080
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db       3143 TATGAATGTAAGGTTTACTGGCCCCAATTTTAGCGGTACGGTTTTCCTGGCCAATACCAA 3202

Qy       1081 CCTTATCCTACACGGTGTAAGCTTCTATGGGTTTAACAATACCTGTGTGGAAGCCTGGAC 1140
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db       3203 CCTTATCCTACACGGTGTAAGCTTCTATGGGTTTAACAATACCTGTGTGGAAGCCTGGAC 3262

Qy       1141 CGATGTAAGGGTTCGGGGCTGTGCCTTTTACTGCTGCTGGAAGGGGGTGGTGTGTCGCCC 1200
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db       3263 CGATGTAAGGGTTCGGGGCTGTGCCTTTTACTGCTGCTGGAAGGGGGTGGTGTGTCGCCC 3322

Qy       1201 CAAAAGCAGGGCTTCAATTAAGAAATGCCTCTTTGAAAGGTGTACCTTGGGTATCCTGTC 1260
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db       3323 CAAAAGCAGGGCTTCAATTAAGAAATGCCTCTTTGAAAGGTGTACCTTGGGTATCCTGTC 3382

Qy       1261 TGAGGGTAACTCCAGGGTGCGCCACAATGTGGCCTCCGACTGTGGTTGCTTCATGCTAGT 1320
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db       3383 TGAGGGTAACTCCAGGGTGCGCCACAATGTGGCCTCCGACTGTGGTTGCTTCATGCTAGT 3442

Qy       1321 GAAAAGCGTGGCTGTGATTAAGCATAACATGGTATGTGGCAACTGCGAGGACAGGGCCTC 1380
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db       3443 GAAAAGCGTGGCTGTGATTAAGCATAACATGGTATGTGGCAACTGCGAGGACAGGGCCTC 3502

Qy       1381 TCAGATGCTGACCTGCTCGGACGGCAACTGTCACCTGCTGAAGACCATTCACGTAGCCAG 1440
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db       3503 TCAGATGCTGACCTGCTCGGACGGCAACTGTCACCTGCTGAAGACCATTCACGTAGCCAG 3562

Qy       1441 CCACTCTCGCAAGGCCTGGCCAGTGTTTGAGCATAACATACTGACCCGCTGTTCCTTGCA 1500
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db       3563 CCACTCTCGCAAGGCCTGGCCAGTGTTTGAGCATAACATACTGACCCGCTGTTCCTTGCA 3622

Qy       1501 TTTGGGTAACAGGAGGGGGGTGTTCCTACCTTACCAATGCAATTTGAGTCACACTAAGAT 1560
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db       3623 TTTGGGTAACAGGAGGGGGGTGTTCCTACCTTACCAATGCAATTTGAGTCACACTAAGAT 3682

Qy       1561 ATTGCTTGAGCCCGAGAGCATGTCCAAGGTGAACCTGAACGGGGTGTTTGACATGACCAT 1620
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db       3683 ATTGCTTGAGCCCGAGAGCATGTCCAAGGTGAACCTGAACGGGGTGTTTGACATGACCAT 3742

Qy       1621 GAAGATCTGGAAGGTGCTGAGGTACGATGAGACCCGCACCAGGTGCAGACCCTGCGAGTG 1680
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db       3743 GAAGATCTGGAAGGTGCTGAGGTACGATGAGACCCGCACCAGGTGCAGACCCTGCGAGTG 3802

Qy       1681 TGGCGGTAAACATATTAGGAACCAGCCTGTGATGCTGGATGTGACCGAGGAGCTGAGGCC 1740
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db       3803 TGGCGGTAAACATATTAGGAACCAGCCTGTGATGCTGGATGTGACCGAGGAGCTGAGGCC 3862

Qy       1741 CGATCACTTGGTGCTGGCCTGCACCCGCGCTGAGTTTGGCTCTAGCGATGAAGATACAGA 1800
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db       3863 CGATCACTTGGTGCTGGCCTGCACCCGCGCTGAGTTTGGCTCTAGCGATGAAGATACAGA 3922

Qy       1801 TTGAGGTACTGAAATGTGTGGGC 1823
              |||||||||||||||||||||||
Db       3923 TTGAGGTACTGAAATGTGTGGGC 3945
```

SEQ ID NO:3 (IRES sequences)

```
RESULT 8
AAC81948
ID   AAC81948 standard; DNA; 1616 BP.
XX
AC   AAC81948;
XX
DT   28-FEB-2001  (first entry)
XX
DE   Backbone transfer vector pSGT5(SDM/RRE1/CM) IRES and puromycin DNA.
XX
KW   Encapsidation; transfer vector; nephrotropic; antiparkinsonian; anti-HIV;
KW   cytostatic; gene therapy; transgenic; retroviral packaging;
KW   gene delivery; Parkinson's disease; infectious diseases; cancer; ds.
XX
OS   Synthetic.
XX
PN   WO200040741-A2.
XX
PD   13-JUL-2000.
XX
PF   06-JAN-2000; 2000WO-US000390.
XX
PR   07-JAN-1999;   99US-0115247P.
XX
PA   (USSH ) US DEPT HEALTH & HUMAN SERVICES.
XX
PI   Arya SK;
XX
DR   WPI; 2000-475836/41.
XX
PT   New lentivirus transfer vector, functionally deleted for a splice donor
PT   site and comprising a packaging signal and transgene operably linked to a
PT   promoter, for improving encapsidation or transgene RNA and for gene
PT   therapy.
XX
PS   Example 1; Page 143; 143pp; English.
XX
CC   This invention describes a novel transfer vector derived from a
CC   lentivirus, functionally deleted for a splice donor site (SD), and
CC   comprising a packaging signal and transgene operably linked to a
CC   promoter. The products of the invention have nephrotropic,
CC   antiparkinsonian, anti-HIV, and cytostatic activity and can be used for
CC   gene therapy. Encapsidation of transgene RNA is improved using the new
CC   retroviral packaging and transfer vectors. The new transfer and packaging
CC   vectors are used as gene delivery agents and allows transfer of a
CC   transgene into the genome of non-dividing cells. They can be used to
CC   create a high-efficiency packaging cell line that provides greatly
CC   enhanced packaging of foreign DNA. Individuals suffering from a
CC   deficiency in alpha-galactosidase expression, such as Fabry disease can
CC   be treated by delivering the vectors to cells in vitro or in vivo.
CC   Parkinson's disease, infectious diseases, such as acquired
CC   immunodeficiency syndrome and cancers can be treated with the vectors.
CC   The non-infective packaging vectors can be used to detect wild-type HIV
CC   in biological samples using southern or northern blot assays. The
CC   packaging of the vector RNA is maximised, without an increase in the
```

```
CC   packaging of the viral RNA. Deletion of sequences upstream and downstream
CC   of the 5' SD region of the HIV-2 packaging vector results in suppressed
CC   encapsidation of the packaging vector genomes without critical loss of
CC   gene expression. Functional deletion of the SD site of the transfer
CC   vector results in enhanced encapsidation of the transfer vector's genome.
CC   HIV-2 packaging vector specifically and faithfully packages its own
CC   optimally constructed transfer vector and gives better quality and titre
CC   of vector than HIV-1
XX
SQ   Sequence 1616 BP; 316 A; 521 C; 471 G; 308 T; 0 U; 0 Other;

  Query Match             100.0%;  Score 605;  DB 1;  Length 1616;
  Best Local Similarity   100.0%;
  Matches  605;  Conservative    0;  Mismatches    0;  Indels    0;  Gaps    0;

Qy          1 TGCATCTAGGGCGGCCAATTCCGCCCCTCTCCCTCCCCCCCCCCTAACGTTACTGGCCGA 60
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        341 TGCATCTAGGGCGGCCAATTCCGCCCCTCTCCCTCCCCCCCCCCTAACGTTACTGGCCGA 400

Qy         61 AGCCGCTTGGAATAAGGCCGGTGTGCGTTTGTCTATATGTGATTTTCCACCATATTGCCG 120
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        401 AGCCGCTTGGAATAAGGCCGGTGTGCGTTTGTCTATATGTGATTTTCCACCATATTGCCG 460

Qy        121 TCTTTTGGCAATGTGAGGGCCCGGAAACCTGGCCCTGTCTTCTTGACGAGCATTCCTAGG 180
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        461 TCTTTTGGCAATGTGAGGGCCCGGAAACCTGGCCCTGTCTTCTTGACGAGCATTCCTAGG 520

Qy        181 GGTCTTTCCCCTCTCGCCAAAGGAATGCAAGGTCTGTTGAATGTCGTGAAGGAAGCAGTT 240
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        521 GGTCTTTCCCCTCTCGCCAAAGGAATGCAAGGTCTGTTGAATGTCGTGAAGGAAGCAGTT 580

Qy        241 CCTCTGGAAGCTTCTTGAAGACAAACAACGTCTGTAGCGACCCTTTGCAGGCAGCGGAAC 300
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        581 CCTCTGGAAGCTTCTTGAAGACAAACAACGTCTGTAGCGACCCTTTGCAGGCAGCGGAAC 640

Qy        301 CCCCCACCTGGCGACAGGTGCCTCTGCGGCCAAAAGCCACGTGTATAAGATACACCTGCA 360
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        641 CCCCCACCTGGCGACAGGTGCCTCTGCGGCCAAAAGCCACGTGTATAAGATACACCTGCA 700

Qy        361 AAGGCGGCACAACCCCAGTGCCACGTTGTGAGTTGGATAGTTGTGGAAAGAGTCAAATGG 420
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        701 AAGGCGGCACAACCCCAGTGCCACGTTGTGAGTTGGATAGTTGTGGAAAGAGTCAAATGG 760

Qy        421 CTCTCCTCAAGCGTATTCAACAAGGGGCTGAAGGATGCCCAGAAGGTACCCCATTGTATG 480
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        761 CTCTCCTCAAGCGTATTCAACAAGGGGCTGAAGGATGCCCAGAAGGTACCCCATTGTATG 820

Qy        481 GGATCTGATCTGGGGCCTCGGTGCACATGCTTTACATGTGTTTAGTCGAGGTTAAAAAAA 540
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        821 GGATCTGATCTGGGGCCTCGGTGCACATGCTTTACATGTGTTTAGTCGAGGTTAAAAAAA 880

Qy        541 CGTCTAGGCCCCCCGAACCACGGGGACGTGGTTTTCCTTTGAAAAACACGATGATAAGCT 600
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        881 CGTCTAGGCCCCCCGAACCACGGGGACGTGGTTTTCCTTTGAAAAACACGATGATAAGCT 940

Qy        601 TGCCA 605
              |||||
Db        941 TGCCA 945
```

SEQ ID No:4 (hTERT promoter)

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RESULT 9
AX003120
LOCUS       AX003120               5126 bp    DNA     linear   PAT 24-AUG-2000
DEFINITION  Sequence 1 from Patent WO9933998.
ACCESSION   AX003120
VERSION     AX003120.1  GI:9926982
KEYWORDS    .
SOURCE      Homo sapiens (human)
  ORGANISM  Homo sapiens
            Eukaryota; Metazoa; Chordata; Craniata; Vertebrata; Euteleostomi;
            Mammalia; Eutheria; Euarchontoglires; Primates; Haplorrhini;
            Catarrhini; Hominidae; Homo.
REFERENCE   1
  AUTHORS   Wick,M. and Hagen,G.
  TITLE     Regulatory dna sequences of the human catalytic telomerase sub-unit
            gene, diagnostic and therapeutic use thereof
  JOURNAL   Patent: WO 9933998-A 1 08-JUL-1999;
            WICK MARESA (DE); BAYER AG (DE)
FEATURES             Location/Qualifiers
     source          1. .5126
                     /organism="Homo sapiens"
                     /mol_type="unassigned DNA"
                     /db_xref="taxon:9606"
ORIGIN

  Query Match             100.0%;  Score 455;  DB 9;  Length 5126;
  Best Local Similarity   100.0%;
  Matches  455;  Conservative    0;  Mismatches    0;  Indels    0;  Gaps    0;

Qy          1 TGGCCCCTCCCTCGGGTTACCCCACAGCCTAGGCCGATTCGACCTCTCTCCGCTGGGGCC 60
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db       4669 TGGCCCCTCCCTCGGGTTACCCCACAGCCTAGGCCGATTCGACCTCTCTCCGCTGGGGCC 4728

Qy         61 CTCGCTGGCGTCCCTGCACCCTGGGAGCGCGAGCGGCGCGCGGGCGGGGAAGCGCGGCCC 120
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db       4729 CTCGCTGGCGTCCCTGCACCCTGGGAGCGCGAGCGGCGCGCGGGCGGGGAAGCGCGGCCC 4788

Qy        121 AGACCCCCGGGTCCGCCCGGAGCAGCTGCGCTGTCGGGGCCAGGCCGGGCTCCCAGTGGA 180
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db       4789 AGACCCCCGGGTCCGCCCGGAGCAGCTGCGCTGTCGGGGCCAGGCCGGGCTCCCAGTGGA 4848

Qy        181 TTCGCGGGCACAGACGCCCAGGACCGCGCTCCCCACGTGGCGGAGGGACTGGGGACCCGG 240
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db       4849 TTCGCGGGCACAGACGCCCAGGACCGCGCTCCCCACGTGGCGGAGGGACTGGGGACCCGG 4908

Qy        241 GCACCCGTCCTGCCCCTTCACCTTCCAGCTCCGCCTCCTCCGCGCGGACCCCGCCCCGTC 300
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db       4909 GCACCCGTCCTGCCCCTTCACCTTCCAGCTCCGCCTCCTCCGCGCGGACCCCGCCCCGTC 4968

Qy        301 CCGACCCCTCCCGGGTCCCCGGCCCAGCCCCCTCCGGGCCCTCCCAGCCCCTCCCCTTCC 360
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db       4969 CCGACCCCTCCCGGGTCCCCGGCCCAGCCCCCTCCGGGCCCTCCCAGCCCCTCCCCTTCC 5028

Qy        361 TTTCCGCGGCCCCGCCCTCTCCTCGCGGCGCGAGTTTCAGGCAGCGCTGCGTCCTGCTGC 420
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db       5029 TTTCCGCGGCCCCGCCCTCTCCTCGCGGCGCGAGTTTCAGGCAGCGCTGCGTCCTGCTGC 5088
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Qy        421 GCACGTGGGAAGCCCTGGCCCCGGCCACCCCCGCG 455
              ||||||||||||||||||||||||||||||||||||
Db       5089 GCACGTGGGAAGCCCTGGCCCCGGCCACCCCCGCG 5123
```

Therefore, it would have been obvious to combine the teachings of Morin et al., with the teachings of Li et al. to arrive at the claimed vector and methods for killing cancer cells, with reasonable expectation of success by substituting AFP promoter taught by Li et al. with hTERT promoter taught by Morin et al. The sequences of E1A gene (SEQ ID No:1), E1B gene (SEQ ID No:2), IRES sequence (SEQ ID No:3), and hTERT promoter (SEQ ID NO:4) are well known in the art and can be obtained from the sequences disclosed by Stuart et al. (WO 2002/20754), Nemerow et al. (WO 2000/42208), Arya (WO 2000/40741), and Hagen et al. (WO 1999/33998) via PCR cloning taught by Morin et al. (See pages 12-14, Morin et al., 2000).

The Examiner would like to direct Applicant's attention to recent decision by U.S. Supreme Court in *KSR International Co. v. Teleflex, Inc.* that forecloses the argument that a **specific** teaching, suggestion, or motivation is an absolute requirement to support a finding of obviousness. See recent Board decision *Ex parte Smith*, --USPQ2d--, slip op. at 20, (Bd. Pat. App. & Interf. June 25, 2007) (citing KSR, 82 USPQ2d at 1936) (available at http://www.uspto.gov/web/offices/dcom/bpai/prec/fd071925.pdf). The Examiner notes that in the instant case, even in the absence of recent decision by U.S. Supreme Court in *KSR International Co. v. Teleflex, Inc.,* the suggestion and motivation to combine Morin et al., Li et al., Stuart et al., Nemerow et al., Arya, and Hagen et al. have been clearly set forth above in this office action.

7. Claims 9, 10, 18, and 19 are rejected under 35 U.S.C. 103(a) as being unpatentable over **Morin et al.** (Morin et al., 2000, WO 00/46355, international publication date, August 10, 2000; this reference is disclosed in IDS filed on 04/25/2006, listed as reference No. BA) in view of **Li et al.** (Li et al., A hepatocellular carcinoma-specific adenovirus variant, CV890, eliminates distant human liver tumors in combination with doxorubicin. *Cancer Res.* 61(17): 6428-36, 2001; this reference is disclosed in IDS filed on 04/25/2006, listed as reference CC), **Stuart et al.** (WO 2002/20754, international publication date 03/14/2002), **Nemerow et al.** (WO 2000/42208, international publication date 07/20/2000), **Arya** (WO 2000/40741, international publication date 07/13/2000), and **Hagen et al.** (WO 1999/33998, international publication date 07/08/1999) as applied to claims 4-8, 11-17, 20, and 21 above, and further in view of **Cheng et al.** (Cheng et al., U.S. patent application No. 2003/0104625, publication date, June 5, 2003; filed Feb. 22, 2002; this reference is cited in the office action dated 06/19/2007). *This rejection is necessitated by claim amendments filed on 11/04/2009.*

The teachings Morin et al., Li et al., Stuart et al., Nemerow et al., Arya, and Hagen et al. have been discussed in the preceding section of the rejection of claims 4-8, 11-17, 20, and 21 and 12 under 35 U.S.C. 103(a) as being unpatentable over Morin et al. in view of Li et al.

None of Morin et al. and either Li et al. teaches various cancer recited in claims 9 and 18, and ostesarcoma and brain tumor recited in claims 10 and 19 of instant application.

However, at the time of filing of instant application, treating a type of cancer cell *in vivo* using adenovirus as an anticancer agent (claims 9, 10, 18, and 19 of instant applicant) was

known in the art. For instant, Cheng et al. teach tumor and normal tissues, including liver, kidney, lung, bone marrow, brain, spleen, and ovary, were collected from various experimental mice groups, which was administered with adenoviral vector (See paragraph [0570], Cheng et al., 2003).

Therefore, it would have been *prima facie* obvious to one having ordinary skill in the art at the time of the invention to incorporate the teachings of Cheng et al. regarding treating various cancer cells using adenovirus as an anticancer with the combined teachings of Morin et al., Li et al., Stuart et al., Nemerow et al., Arya, and Hagen et al. regarding administration of polynucleotide comprising E1A-IRES-E1B cassette expressed under the control of hTERT promoter for lysis of cancer cells to arrive at the method of killing brain cancer cells *in vitro* comprising the step of administering recombinant virus comprising polynucleotide E1A-IRES-E1B cassette expressed via the control of hTERT promoter, as recited in claims 9 and 10 of instant application.

One having ordinary skill in the art would have been motivated to incorporate the teachings of Cheng et al. regarding treating various cancer cells with adenovirus with the combined teachings of Morin et al., Li et al., Stuart et al., Nemerow et al., Arya, and Hagen et al. regarding administration of polynucleotide comprising E1A-IRES-E1B cassette expressed via the control of hTERT promoter for killing cancer cells because Morin et al teaches the activity of hTERT promoter is highly specific for cancer cells, which includes brain cancer cells taught by Change et al.

There would have been a reasonable expectation of success given (i) successful demonstration of expression of E1A-IRES-E1B cassette under both transcriptional control of

human TERT promoter, by the teachings of Morin et al, and translational control, by the teachings of Li et al. for killing cancer cells via intratumoral administration, and F1A gene, E1B gene, IRES, and hTERT promoter sequences disclosed by Stuart et al., Nemerow et al., Arya, and Hagen et al. respectively, and (ii) the demonstration of hTERT promoter control the transcription of adenovirus E4 gene by Cheng et al. (See Figure 49, Change et al.)

Thus, the claimed invention as a whole was clearly *prima facie* obvious.

8. Claims 4-21 are rejected under 35 U.S.C. 103(a) as being unpatentable over **Morin et al.** (Morin et al., 2000, WO 00/46355, international publication date, August 10, 2000; this reference is disclosed in IDS filed on 04/25/2006, listed as reference No. BA) in view of **Yu et al.** (US 6,692,736, issued on 02/17/2004, filed on 03/21/2001) **Stuart et al.** (WO 2002/20754, international publication date 03/14/2002), **Nemerow et al.** (WO 2000/42208, international publication date 07/20/2000), **Arya** (WO 2000/40741, international publication date 07/13/2000), and **Hagen et al.** (WO 1999/33998, international publication date 07/08/1999). *This rejection is necessitated by claim amendments filed on 11/04/2009.*

It is noted that Stuart et al. (WO 2002/20754, 686 pages), Nemerow et al. (WO 2000/42208, 212 pages), Arya (WO 2000/40741, 144 pages), and Hagen et al. (WO 1999/33998, 100 pages) are relied on respectively for the disclosure of SEQ D No: 1, SEQ D No: 2, SEQ ID No: 3, and SEQ ID No: 4 of instant application. Only cover pages from each of these four references are included along with this office action. The sequence alignments are provided below in this office action.

Amended claim 4 filed on 11/04/2009 reads as follows: A polynucleotide cassette comprising an hTERT promoter operably linked with an E1A gene, an IRES sequence, and an E1B gene in this order, wherein the cassette is capable of replicating in a local cancer area, and wherein the hTERT promoter consists of the nucleotide sequence of SEQ ID NO: 4, the E1A gene consists of the nucleotide sequence of SEQ ID NO: 1, the IRES sequence consists of the nucleotide sequence of SEQ ID NO: 3, and the E1B gene consists of the nucleotide sequence of SEQ ID NO: 2.

Amended claim 8 filed on 11/04/2009 reads as follows: A method of killing cancer cells, comprising the step of: locally administering an effective amount of the recombinant virus according to claim 5 to a patient in need thereof, such that the recombinant virus is capable of replicating in a local cancer area of the patient, and wherein replication of the recombinant virus kills the cancer cell in the local cancer area.

Newly added claim 13 filed on 11/04/2009 reads as follows: A polynucleotide cassette comprising an hTERT promoter operably linked with an E1A gene, an IRES sequence, and an E1B gene in this order, wherein the cassette is capable of replicating in a cancer cell, and wherein the hTERT promoter consists of the nucleotide sequence of SEQ ID NO: 4, the E1A gene consists of the nucleotide sequence of SEQ ID NO: 1, the IRES sequence consists of the nucleotide sequence of SEQ ID NO: 3, and the E1B gene consists of the nucleotide sequence of SEQ ID NO: 2.

Newly added claim 17 filed on 11/04/2009 reads as follows: A method of killing cancer cells, comprising the step of: administering an effective amount of the recombinant virus according to claim 14 to a patient in need thereof, such that the recombinant virus is capable of replicating in a cancer cell of the patient, and wherein replication of the recombinant virus kills the cancer cell.

Morin et al. (2000) discloses use of the hTERT promoter to selectively direct expression in cancer cells. More specifically, Morin et al., 2000 taught oncolytic viruses, in which a toxin or a genetic element essential for viral replication is placed under control of the TERT promoter. Thereby, the virus that replicates preferentially in cells expressing TERT, and thereby selectively

lyses cancer cells (See *in vitro* Example 4 on transfected human cell lines, pages 35-36, and *in situ* Example 3 on transplanted human tumor 143B cells on nude mice, page 35, Morin et al., 2000).

While Morin et al. does not teach an adenovirus with IRES inserted between E1A and E1B in an adenovirus to be administered and replicated locally as recited in claims 4 and 8 of instant application, operably linked to the hTERT promoter, **Yu et al.** teaches cell-specific adenovirus vector comprising target cell-specific TRE (transcriptional regulatory element) operably linked to E1A-IRES-E1B and intratumoral administration of the adenoviral vector, whose replication leads destruction of xenografts of cancer cells grown in a mouse (See Figures 1and 2, lines 12-16 of column 61, lines 8-17 of column 63, Yu et al.).

With regard to cancer recited in claims 9, 10, 18, and 19, Yu et al. teaches hepatocellular carcinoma (HCC) cells, gonadal and other germ cell tumors (especially endodermal sinus tumors), brain tumor cells, ovarian tumor cells, acinar cell carcinoma of the pancreas, primary gall bladder tumor, uterine endometrial adenocarcinoma, and any metastases of the foregoing (which can occur in lung, adrenal gland, bone marrow, and/or spleen). Yu et al teaches that in some cases, metastatic disease to the liver from certain pancreatic and stomach cancers produce AFP, especially preferred as target cells for an AFP-TRE are hepatocellular carcinoma cells and any of their metastases (See bridging paragraph of columns 27-28, Yu et al.).

While Morin et al. do not teach "wherein the hTERT promoter consists of the nucleotide sequence of SEQ ID NO: 4, the E1A gene consists of the nucleotide sequence of SEQ ID NO: 1, the IRES sequence consists of the nucleotide sequence of SEQ ID NO: 3, and the E1B gene consists of the nucleotide sequence of SEQ ID NO: 2" recited in claims 4 and 13, **Stuart et al.**

(WO 2002/20754) teaches sequences matches 100% to SEQ ID NO:1 of instant application, **Nemerow** (WO 2000/42208) teaches sequences match 100% to SEQ ID No:2 of instant application, **Arya** (WO 2000/40741) teaches sequences match 100% to SEQ ID No:3 of instant application, and Hagen et al. (WO 1999/33998) teaches sequences match 100% to SEQ ID No: 4 of instant application. The sequence alignments of SEQ ID No: 1-4 of instant application to the sequences disclosed in the respective prior arts are provided below.

SEQ ID No: 1 (E1A gene)

```
RESULT 8
ABK71579
ID   ABK71579 standard; cDNA; 1247 BP.
XX
AC   ABK71579;
XX
DT   30-JUL-2002  (first entry)
XX
DE   Human dithp polynucleotide #45.
XX
KW   Human; dithp; diagnostic and therapeutic polynucleotide; gene; ss; bone;
KW   cell proliferative disorder; cancer; tumour; autoimmune disorder; brain;
KW   inflammatory disorder; viral infection; bacterial infection; seizure;
KW   fungal infection; parasitic infections; developmental disorder; breast;
KW   endocrine disorder; metabolic disorder; neurological disorder; cervix;
KW   gastrointestinal disorder; transport disorder; gene therapy; kidney;
KW   adrenal gland; bone marrow; lung; ovary; pancreas; prostate; spleen;
KW   skin; testis; thymus.
XX
OS   Homo sapiens.
XX
PN   WO200220754-A2.
XX
PD   14-MAR-2002.
XX
PF   29-AUG-2001; 2001WO-US027127.
XX
PR   05-SEP-2000; 2000US-0229747P.
PR   05-SEP-2000; 2000US-0229748P.
PR   05-SEP-2000; 2000US-0229749P.
PR   05-SEP-2000; 2000US-0229750P.
PR   05-SEP-2000; 2000US-0229751P.
PR   05-SEP-2000; 2000US-0230583P.
PR   06-SEP-2000; 2000US-0230505P.
PR   06-SEP-2000; 2000US-0230514P.
PR   06-SEP-2000; 2000US-0230515P.
PR   06-SEP-2000; 2000US-0230517P.
PR   06-SEP-2000; 2000US-0230518P.
PR   06-SEP-2000; 2000US-0230519P.
PR   06-SEP-2000; 2000US-0230595P.
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PR 06-SEP-2000; 2000US-0230597P.
PR 06-SEP-2000; 2000US-0230598P.
PR 06-SEP-2000; 2000US-0230599P.
PR 06-SEP-2000; 2000US-0230610P.
PR 06-SEP-2000; 2000US-0230865P.
PR 06-SEP-2000; 2000US-0230988P.
PR 07-SEP-2000; 2000US-0230951P.
PR 07-SEP-2000; 2000US-0231163P.
PR 07-SEP-2000; 2000US-0231167P.
XX
PA (INCY-) INCYTE GENOMICS INC.
XX
PI Stuart J, Lincoln SE, Altus CM, Dufour GE, Chalup MS, Hillman JL;
PI Jones AL, Yu JY, Wright RJ, Gietzen D, Liu TF, Yap PE, Dahl CR;
PI Momiyama MG, Bradley DL, Rohatgi SD, Harris B, Roseberry AM;
PI Gerstin EH, Peralta CH, David MH, Panzer SR, Flores V, Daffo A;
PI Marwaha R, Chen AJ, Chang SC, Au AP, Inman RR;
XX
DR WPI; 2002-383054/41.
DR P-PSDB; ABG59987.
XX
PT An isolated polynucleotide useful in diagnostics and therapeutics.
XX
PS Claim 1; Page 427-428; 686pp; English.
XX
CC The invention relates to human diagnostic and therapeutic (dithp)
CC polynucleotides and their associated polypeptides (DITHP polypeptides).
CC The sequences of the invention are used in the treatment and diagnosis of
CC cell proliferative disorders (e.g. atherosclerosis, cirrhosis), cancers
CC (e.g. tumours of the adrenal gland, bone, bone marrow, brain, breast,
CC cervix, kidney, lung, ovary, pancreas, prostate, skin, spleen, testis or
CC thymus), autoimmune/inflammatory disorders (e.g. asthma, bronchitis,
CC psoriasis, osteoporosis), viral infections, bacterial infections, fungal
CC infections, parasitic infections, developmental disorders (e.g. anaemia,
CC epilepsy), seizure disorders (e.g. cerebral palsy, spina bifida),
CC endocrine disorders (e.g. thrombosis, aneurysm), metabolic disorders
CC (e.g. obesity, diabetes), neurological disorders (e.g. stroke,
CC amyotrophic lateral sclerosis, multiple sclerosis), gastrointestinal
CC disorders (e.g. ulcerative colitis, lysinuria) and transport disorders
CC (e.g. myotonic dystrophy, catatonia, peripheral neuropathy). Sequences
CC ABK71535-ABK71809 represent human dithp polynucleotides of the invention
XX
SQ Sequence 1247 BP; 270 A; 308 C; 344 G; 325 T; 0 U; 0 Other;

Query Match 100.0%; Score 899; DB 1; Length 1247;
Best Local Similarity 100.0%;
Matches 899; Conservative 0; Mismatches 0; Indels 0; Gaps 0;

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Qy          1 ACACCGGGACTGAAAATGAGACATATTATCTGCCACGGAGGTGTTATTACCGAAGAAATG 60
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        282 ACACCGGGACTGAAAATGAGACATATTATCTGCCACGGAGGTGTTATTACCGAAGAAATG 341

Qy         61 GCCGCCAGTCTTTTGGACCAGCTGATCGAAGAGGTACTGGCTGATAATCTTCCACCTCCT 120
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        342 GCCGCCAGTCTTTTGGACCAGCTGATCGAAGAGGTACTGGCTGATAATCTTCCACCTCCT 401

Qy        121 AGCCATTTTGAACCACCTACCCTTCACGAACTGTATGATTTAGACGTGACGGCCCCCGAA 180
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        402 AGCCATTTTGAACCACCTACCCTTCACGAACTGTATGATTTAGACGTGACGGCCCCCGAA 461
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Qy        181 GATCCCAACGAGGAGGCGGTTTCGCAGATTTTTCCCGACTCTGTAATGTTGGCGGTGCAG 240
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        462 GATCCCAACGAGGAGGCGGTTTCGCAGATTTTTCCCGACTCTGTAATGTTGGCGGTGCAG 521

Qy        241 GAAGGGATTGACTTACTCACTTTTCCGCCGGCGCCCGGTTCTCCGGAGCCGCCTCACCTT 300
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        522 GAAGGGATTGACTTACTCACTTTTCCGCCGGCGCCCGGTTCTCCGGAGCCGCCTCACCTT 581

Qy        301 TCCCGGCAGCCCGAGCAGCCGGAGCAGAGAGCCTTGGGTCCGGTTTCTATGCCAAACCTT 360
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        582 TCCCGGCAGCCCGAGCAGCCGGAGCAGAGAGCCTTGGGTCCGGTTTCTATGCCAAACCTT 641

Qy        361 GTACCGGAGGTGATCGATCTTACCTGCCACGAGGCTGGCTTTCCACCCAGTGACGACGAG 420
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        642 GTACCGGAGGTGATCGATCTTACCTGCCACGAGGCTGGCTTTCCACCCAGTGACGACGAG 701

Qy        421 GATGAAGAGGGTGAGGAGTTTGTGTTAGATTATGTGGAGCACCCCGGGCACGGTTGCAGG 480
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        702 GATGAAGAGGGTGAGGAGTTTGTGTTAGATTATGTGGAGCACCCCGGGCACGGTTGCAGG 761

Qy        481 TCTTGTCATTATCACCGGAGGAATACGGGGGACCCAGATATTATGTGTTCGCTTTGCTAT 540
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        762 TCTTGTCATTATCACCGGAGGAATACGGGGGACCCAGATATTATGTGTTCGCTTTGCTAT 821

Qy        541 ATGAGGACCTGTGGCATGTTTGTCTACAGTCCTGTGTCTGAACCTGAGCCTGAGCCCGAG 600
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        822 ATGAGGACCTGTGGCATGTTTGTCTACAGTCCTGTGTCTGAACCTGAGCCTGAGCCCGAG 881

Qy        601 CCAGAACCGGAGCCTGCAAGACCTACCCGCCGTCCTAAAATGGCGCCTGCTATCCTGAGA 660
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        882 CCAGAACCGGAGCCTGCAAGACCTACCCGCCGTCCTAAAATGGCGCCTGCTATCCTGAGA 941

Qy        661 CGCCCGACATCACCTGTGTCTAGAGAATGCAATAGTAGTACGGATAGCTGTGACTCCGGT 720
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        942 CGCCCGACATCACCTGTGTCTAGAGAATGCAATAGTAGTACGGATAGCTGTGACTCCGGT 1001

Qy        721 CCTTCTAACACACCTCCTGAGATACACCCGGTGGTCCCGCTGTGCCCCATTAAACCAGTT 780
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db       1002 CCTTCTAACACACCTCCTGAGATACACCCGGTGGTCCCGCTGTGCCCCATTAAACCAGTT 1061

Qy        781 GCCGTGAGAGTTGGTGGGCGTCGCCAGGCTGTGGAATGTATCGAGGACTTGCTTAACGAG 840
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db       1062 GCCGTGAGAGTTGGTGGGCGTCGCCAGGCTGTGGAATGTATCGAGGACTTGCTTAACGAG 1121

Qy        841 CCTGGGCAACCTTTGGACTTGAGCTGTAAACGCCCCAGGCCATAAGGTGTAAACCTGTG 899
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db       1122 CCTGGGCAACCTTTGGACTTGAGCTGTAAACGCCCCAGGCCATAAGGTGTAAACCTGTG 1180
```

SEQ ID NO: 2 (E1B gene)

```
RESULT 15
AAA59076
ID   AAA59076 standard; DNA; 7607 BP.
XX
AC   AAA59076;
XX
DT   07-NOV-2000  (first entry)
XX
DE   Nucleotide sequence of plasmid GRE5-E1-SV40-Hygro.
```

```
XX
KW   Adenovirus; tripartite leader; adenovirus vector particle; gene delivery;
KW   ss.
XX
OS   Synthetic.
XX
PN   WO200042208-A1.
XX
PD   20-JUL-2000.
XX
PF   14-JAN-2000; 2000WO-EP000265.
XX
PR   14-JAN-1999;   99US-0115920P.
XX
PA   (NOVS ) NOVARTIS AG.
PA   (NOVS ) NOVARTIS-ERFINDUNGEN VERW GES MBH.
PA   (SCRI ) SCRIPPS RES INST.
XX
PI   Nemerow GR,  Von Seggern DJ,  Hallenbeck PL,  Stevenson SC;
PI   Skripchenko Y;
XX
DR   WPI; 2000-476068/41.
XX
PT   New nucleic acid comprising an adenovirus tripartite leader nucleotide
PT   for producing high-capacity and targeted vectors for adenovirus-based
PT   gene therapy.
XX
PS   Example 6; Page 190-192; 212pp; English.
XX
CC   The specification describes a nucleic acid molecule comprising an
CC   adenovirus (AV) tripartite leader (TPL) nucleotide with a sequence
CC   comprising two different TPL exons or three same or different TPL exons.
CC   The nucleic acid is used to produce an adenovirus vector particle,
CC   deliver an exogenous gene to a target cell, pseudotype recombinant viral
CC   vectors, target an adenovirus vector to a cell, produce a modified
CC   adenovirus, deliver a heterologous gene to an animal and produce a
CC   gutless adenoviral vector particle. The present sequence represents
CC   plasmid GRE5-E1-SV40-Hygro, which is used in the course of the invention
XX
SQ   Sequence 7607 BP; 1838 A; 1733 C; 2001 G; 2035 T; 0 U; 0 Other;

  Query Match             100.0%;  Score 1823;  DB 1;  Length 7607;
  Best Local Similarity   100.0%;
  Matches 1823;  Conservative    0;  Mismatches    0;  Indels    0;  Gaps    0;

Qy          1 CTGACCTCATGGAGGCTTGGGAGTGTTTGGAAGATTTTTCTGCTGTGCGTAACTTGCTGG 60
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db       2123 CTGACCTCATGGAGGCTTGGGAGTGTTTGGAAGATTTTTCTGCTGTGCGTAACTTGCTGG 2182

Qy         61 AACAGAGCTCTAACAGTACCTCTTGGTTTTGGAGGTTTCTGTGGGGCTCATCCCAGGCAA 120
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db       2183 AACAGAGCTCTAACAGTACCTCTTGGTTTTGGAGGTTTCTGTGGGGCTCATCCCAGGCAA 2242

Qy        121 AGTTAGTCTGCAGAATTAAGGAGGATTACAAGTGGGAATTTGAAGAGCTTTTGAAATCCT 180
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db       2243 AGTTAGTCTGCAGAATTAAGGAGGATTACAAGTGGGAATTTGAAGAGCTTTTGAAATCCT 2302

Qy        181 GTGGTGAGCTGTTTGATTCTTTGAATCTGGGTCACCAGGCGCTTTTCCAAGAGAAGGTCA 240
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db       2303 GTGGTGAGCTGTTTGATTCTTTGAATCTGGGTCACCAGGCGCTTTTCCAAGAGAAGGTCA 2362
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Qy        241 TCAAGACTTTGGATTTTTCCACACCGGGGCGCGCTGCGGCTGCTGTTGCTTTTTTGAGTT 300
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db       2363 TCAAGACTTTGGATTTTTCCACACCGGGGCGCGCTGCGGCTGCTGTTGCTTTTTTGAGTT 2422

Qy        301 TTATAAAGGATAAATGGAGCGAAGAAACCCATCTGAGCGGGGGGTACCTGCTGGATTTTC 360
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db       2423 TTATAAAGGATAAATGGAGCGAAGAAACCCATCTGAGCGGGGGGTACCTGCTGGATTTTC 2482

Qy        361 TGGCCATGCATCTGTGGAGAGCGGTTGTGAGACACAAGAATCGCCTGCTACTGTTGTCTT 420
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db       2483 TGGCCATGCATCTGTGGAGAGCGGTTGTGAGACACAAGAATCGCCTGCTACTGTTGTCTT 2542

Qy        421 CCGTCCGCCCGGCGATAATACCGACGGAGGAGCAGCAGCAGCAGCAGGAGGAAGCCAGGC 480
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db       2543 CCGTCCGCCCGGCGATAATACCGACGGAGGAGCAGCAGCAGCAGCAGGAGGAAGCCAGGC 2602

Qy        481 GGCGGCGGCAGGAGCAGAGCCCATGGAACCCGAGAGCCGGCCTGGACCCTCGGGAATGAA 540
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db       2603 GGCGGCGGCAGGAGCAGAGCCCATGGAACCCGAGAGCCGGCCTGGACCCTCGGGAATGAA 2662

Qy        541 TGTTGTACAGGTGGCTGAACTGTATCCAGAACTGAGACGCATTTTGACAATTACAGAGGA 600
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db       2663 TGTTGTACAGGTGGCTGAACTGTATCCAGAACTGAGACGCATTTTGACAATTACAGAGGA 2722

Qy        601 TGGGCAGGGGCTAAAGGGGGTAAAGAGGGAGCGGGGGGCTTGTGAGGCTACAGAGGAGGC 660
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db       2723 TGGGCAGGGGCTAAAGGGGGTAAAGAGGGAGCGGGGGGCTTGTGAGGCTACAGAGGAGGC 2782

Qy        661 TAGGAATCTAGCTTTTAGCTTAATGACCAGACACCGTCCTGAGTGTATTACTTTTCAACA 720
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db       2783 TAGGAATCTAGCTTTTAGCTTAATGACCAGACACCGTCCTGAGTGTATTACTTTTCAACA 2842

Qy        721 GATCAAGGATAATTGCGCTAATGAGCTTGATCTGCTGGCGCAGAAGTATTCCATAGAGCA 780
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db       2843 GATCAAGGATAATTGCGCTAATGAGCTTGATCTGCTGGCGCAGAAGTATTCCATAGAGCA 2902

Qy        781 GCTGACCACTTACTGGCTGCAGCCAGGGGATGATTTTGAGGAGGCTATTAGGGTATATGC 840
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db       2903 GCTGACCACTTACTGGCTGCAGCCAGGGGATGATTTTGAGGAGGCTATTAGGGTATATGC 2962

Qy        841 AAAGGTGGCACTTAGGCCAGATTGCAAGTACAAGATCAGCAAACTTGTAAATATCAGGAA 900
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db       2963 AAAGGTGGCACTTAGGCCAGATTGCAAGTACAAGATCAGCAAACTTGTAAATATCAGGAA 3022

Qy        901 TTGTTGCTACATTTCTGGGAACGGGGCCGAGGTGGAGATAGATACGGAGGATAGGGTGGC 960
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db       3023 TTGTTGCTACATTTCTGGGAACGGGGCCGAGGTGGAGATAGATACGGAGGATAGGGTGGC 3082

Qy        961 CTTTAGATGTAGCATGATAAATATGTGGCCGGGGGTGCTTGGCATGGACGGGGTGGTTAT 1020
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db       3083 CTTTAGATGTAGCATGATAAATATGTGGCCGGGGGTGCTTGGCATGGACGGGGTGGTTAT 3142

Qy       1021 TATGAATGTAAGGTTTACTGGCCCCAATTTTAGCGGTACGGTTTTCCTGGCCAATACCAA 1080
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db       3143 TATGAATGTAAGGTTTACTGGCCCCAATTTTAGCGGTACGGTTTTCCTGGCCAATACCAA 3202

Qy       1081 CCTTATCCTACACGGTGTAAGCTTCTATGGGTTTAACAATACCTGTGTGGAAGCCTGGAC 1140
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db       3203 CCTTATCCTACACGGTGTAAGCTTCTATGGGTTTAACAATACCTGTGTGGAAGCCTGGAC 3262
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Qy       1141 CGATGTAAGGGTTCGGGGCTGTGCCTTTTACTGCTGCTGGAAGGGGGTGGTGTGTCGCCC 1200
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db       3263 CGATGTAAGGGTTCGGGGCTGTGCCTTTTACTGCTGCTGGAAGGGGGTGGTGTGTCGCCC 3322

Qy       1201 CAAAAGCAGGGCTTCAATTAAGAAATGCCTCTTTGAAAGGTGTACCTTGGGTATCCTGTC 1260
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db       3323 CAAAAGCAGGGCTTCAATTAAGAAATGCCTCTTTGAAAGGTGTACCTTGGGTATCCTGTC 3382

Qy       1261 TGAGGGTAACTCCAGGGTGCGCCACAATGTGGCCTCCGACTGTGGTTGCTTCATGCTAGT 1320
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db       3383 TGAGGGTAACTCCAGGGTGCGCCACAATGTGGCCTCCGACTGTGGTTGCTTCATGCTAGT 3442

Qy       1321 GAAAAGCGTGGCTGTGATTAAGCATAACATGGTATGTGGCAACTGCGAGGACAGGGCCTC 1380
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db       3443 GAAAAGCGTGGCTGTGATTAAGCATAACATGGTATGTGGCAACTGCGAGGACAGGGCCTC 3502

Qy       1381 TCAGATGCTGACCTGCTCGGACGGCAACTGTCACCTGCTGAAGACCATTCACGTAGCCAG 1440
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db       3503 TCAGATGCTGACCTGCTCGGACGGCAACTGTCACCTGCTGAAGACCATTCACGTAGCCAG 3562

Qy       1441 CCACTCTCGCAAGGCCTGGCCAGTGTTTGAGCATAACATACTGACCCGCTGTTCCTTGCA 1500
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db       3563 CCACTCTCGCAAGGCCTGGCCAGTGTTTGAGCATAACATACTGACCCGCTGTTCCTTGCA 3622

Qy       1501 TTTGGGTAACAGGAGGGGGGTGTTCCTACCTTACCAATGCAATTTGAGTCACACTAAGAT 1560
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db       3623 TTTGGGTAACAGGAGGGGGGTGTTCCTACCTTACCAATGCAATTTGAGTCACACTAAGAT 3682

Qy       1561 ATTGCTTGAGCCCGAGAGCATGTCCAAGGTGAACCTGAACGGGGTGTTTGACATGACCAT 1620
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db       3683 ATTGCTTGAGCCCGAGAGCATGTCCAAGGTGAACCTGAACGGGGTGTTTGACATGACCAT 3742

Qy       1621 GAAGATCTGGAAGGTGCTGAGGTACGATGAGACCCGCACCAGGTGCAGACCCTGCGAGTG 1680
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db       3743 GAAGATCTGGAAGGTGCTGAGGTACGATGAGACCCGCACCAGGTGCAGACCCTGCGAGTG 3802

Qy       1681 TGGCGGTAAACATATTAGGAACCAGCCTGTGATGCTGGATGTGACCGAGGAGCTGAGGCC 1740
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db       3803 TGGCGGTAAACATATTAGGAACCAGCCTGTGATGCTGGATGTGACCGAGGAGCTGAGGCC 3862

Qy       1741 CGATCACTTGGTGCTGGCCTGCACCCGCGCTGAGTTTGGCTCTAGCGATGAAGATACAGA 1800
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db       3863 CGATCACTTGGTGCTGGCCTGCACCCGCGCTGAGTTTGGCTCTAGCGATGAAGATACAGA 3922

Qy       1801 TTGAGGTACTGAAATGTGTGGGC 1823
              |||||||||||||||||||||||
Db       3923 TTGAGGTACTGAAATGTGTGGGC 3945
```

SEQ ID NO:3 (IRES sequences)

```
RESULT 8
AAC81948
ID   AAC81948 standard; DNA; 1616 BP.
XX
AC   AAC81948;
XX
```

```
DT   28-FEB-2001  (first entry)
XX
DE   Backbone transfer vector pSGT5(SDM/RRE1/CM) IRES and puromycin DNA.
XX
KW   Encapsidation; transfer vector; nephrotropic; antiparkinsonian; anti-HIV;
KW   cytostatic; gene therapy; transgenic; retroviral packaging;
KW   gene delivery; Parkinson's disease; infectious diseases; cancer; ds.
XX
OS   Synthetic.
XX
PN   WO200040741-A2.
XX
PD   13-JUL-2000.
XX
PF   06-JAN-2000; 2000WO-US000390.
XX
PR   07-JAN-1999;   99US-0115247P.
XX
PA   (USSH ) US DEPT HEALTH & HUMAN SERVICES.
XX
PI   Arya SK;
XX
DR   WPI; 2000-475836/41.
XX
PT   New lentivirus transfer vector, functionally deleted for a splice donor
PT   site and comprising a packaging signal and transgene operably linked to a
PT   promoter, for improving encapsidation or transgene RNA and for gene
PT   therapy.
XX
PS   Example 1; Page 143; 143pp; English.
XX
CC   This invention describes a novel transfer vector derived from a
CC   lentivirus, functionally deleted for a splice donor site (SD), and
CC   comprising a packaging signal and transgene operably linked to a
CC   promoter. The products of the invention have nephrotropic,
CC   antiparkinsonian, anti-HIV, and cytostatic activity and can be used for
CC   gene therapy. Encapsidation of transgene RNA is improved using the new
CC   retroviral packaging and transfer vectors. The new transfer and packaging
CC   vectors are used as gene delivery agents and allows transfer of a
CC   transgene into the genome of non-dividing cells. They can be used to
CC   create a high-efficiency packaging cell line that provides greatly
CC   enhanced packaging of foreign DNA. Individuals suffering from a
CC   deficiency in alpha-galactosidase expression, such as Fabry disease can
CC   be treated by delivering the vectors to cells in vitro or in vivo.
CC   Parkinson's disease, infectious diseases, such as acquired
CC   immunodeficiency syndrome and cancers can be treated with the vectors.
CC   The non-infective packaging vectors can be used to detect wild-type HIV
CC   in biological samples using southern or northern blot assays. The
CC   packaging of the vector RNA is maximised, without an increase in the
CC   packaging of the viral RNA. Deletion of sequences upstream and downstream
CC   of the 5' SD region of the HIV-2 packaging vector results in suppressed
CC   encapsidation of the packaging vector genomes without critical loss of
CC   gene expression. Functional deletion of the SD site of the transfer
CC   vector results in enhanced encapsidation of the transfer vector's genome.
CC   HIV-2 packaging vector specifically and faithfully packages its own
CC   optimally constructed transfer vector and gives better quality and titre
CC   of vector than HIV-1
XX
SQ   Sequence 1616 BP; 316 A; 521 C; 471 G; 308 T; 0 U; 0 Other;
```

```
  Query Match             100.0%;  Score 605;  DB 1;  Length 1616;
  Best Local Similarity   100.0%;
  Matches  605;  Conservative    0;  Mismatches    0;  Indels    0;  Gaps    0;

Qy          1 TGCATCTAGGGCGGCCAATTCCGCCCCTCTCCCTCCCCCCCCCCTAACGTTACTGGCCGA 60
              |||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        341 TGCATCTAGGGCGGCCAATTCCGCCCCTCTCCCTCCCCCCCCCCTAACGTTACTGGCCGA 400

Qy         61 AGCCGCTTGGAATAAGGCCGGTGTGCGTTTGTCTATATGTGATTTTCCACCATATTGCCG 120
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        401 AGCCGCTTGGAATAAGGCCGGTGTGCGTTTGTCTATATGTGATTTTCCACCATATTGCCG 460

Qy        121 TCTTTTGGCAATGTGAGGGCCCGGAAACCTGGCCCTGTCTTCTTGACGAGCATTCCTAGG 180
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        461 TCTTTTGGCAATGTGAGGGCCCGGAAACCTGGCCCTGTCTTCTTGACGAGCATTCCTAGG 520

Qy        181 GGTCTTTCCCCTCTCGCCAAAGGAATGCAAGGTCTGTTGAATGTCGTGAAGGAAGCAGTT 240
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        521 GGTCTTTCCCCTCTCGCCAAAGGAATGCAAGGTCTGTTGAATGTCGTGAAGGAAGCAGTT 580

Qy        241 CCTCTGGAAGCTTCTTGAAGACAAACAACGTCTGTAGCGACCCTTTGCAGGCAGCGGAAC 300
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        581 CCTCTGGAAGCTTCTTGAAGACAAACAACGTCTGTAGCGACCCTTTGCAGGCAGCGGAAC 640

Qy        301 CCCCCACCTGGCGACAGGTGCCTCTGCGGCCAAAAGCCACGTGTATAAGATACACCTGCA 360
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        641 CCCCCACCTGGCGACAGGTGCCTCTGCGGCCAAAAGCCACGTGTATAAGATACACCTGCA 700

Qy        361 AAGGCGGCACAACCCCAGTGCCACGTTGTGAGTTGGATAGTTGTGGAAAGAGTCAAATGG 420
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        701 AAGGCGGCACAACCCCAGTGCCACGTTGTGAGTTGGATAGTTGTGGAAAGAGTCAAATGG 760

Qy        421 CTCTCCTCAAGCGTATTCAACAAGGGGCTGAAGGATGCCCAGAAGGTACCCCATTGTATG 480
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        761 CTCTCCTCAAGCGTATTCAACAAGGGGCTGAAGGATGCCCAGAAGGTACCCCATTGTATG 820

Qy        481 GGATCTGATCTGGGGCCTCGGTGCACATGCTTTACATGTGTTTAGTCGAGGTTAAAAAAA 540
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        821 GGATCTGATCTGGGGCCTCGGTGCACATGCTTTACATGTGTTTAGTCGAGGTTAAAAAAA 880

Qy        541 CGTCTAGGCCCCCCGAACCACGGGGACGTGGTTTTCCTTTGAAAAACACGATGATAAGCT 600
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        881 CGTCTAGGCCCCCCGAACCACGGGGACGTGGTTTTCCTTTGAAAAACACGATGATAAGCT 940

Qy        601 TGCCA 605
              |||||
Db        941 TGCCA 945
```

SEQ ID No:4 (hTERT promoter)

```
RESULT 9
AX003120
LOCUS       AX003120               5126 bp    DNA     linear   PAT 24-AUG-2000
DEFINITION  Sequence 1 from Patent WO9933998.
ACCESSION   AX003120
VERSION     AX003120.1  GI:9926982
KEYWORDS    .
SOURCE      Homo sapiens (human)
```

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  ORGANISM  Homo sapiens
            Eukaryota; Metazoa; Chordata; Craniata; Vertebrata; Euteleostomi;
            Mammalia; Eutheria; Euarchontoglires; Primates; Haplorrhini;
            Catarrhini; Hominidae; Homo.
REFERENCE   1
  AUTHORS   Wick,M. and Hagen,G.
  TITLE     Regulatory dna sequences of the human catalytic telomerase sub-unit
            gene, diagnostic and therapeutic use thereof
  JOURNAL   Patent: WO 9933998-A 1 08-JUL-1999;
            WICK MARESA (DE); BAYER AG (DE)
FEATURES             Location/Qualifiers
     source          1. .5126
                     /organism="Homo sapiens"
                     /mol_type="unassigned DNA"
                     /db_xref="taxon:9606"
ORIGIN

  Query Match             100.0%;  Score 455;  DB 9;  Length 5126;
  Best Local Similarity   100.0%;
  Matches  455;  Conservative    0;  Mismatches    0;  Indels    0;  Gaps    0;

Qy          1 TGGCCCCTCCCTCGGGTTACCCCACAGCCTAGGCCGATTCGACCTCTCTCCGCTGGGGCC 60
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db       4669 TGGCCCCTCCCTCGGGTTACCCCACAGCCTAGGCCGATTCGACCTCTCTCCGCTGGGGCC 4728

Qy         61 CTCGCTGGCGTCCCTGCACCCTGGGAGCGCGAGCGGCGCGCGGGCGGGGAAGCGCGGCCC 120
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db       4729 CTCGCTGGCGTCCCTGCACCCTGGGAGCGCGAGCGGCGCGCGGGCGGGGAAGCGCGGCCC 4788

Qy        121 AGACCCCCGGGTCCGCCCGGAGCAGCTGCGCTGTCGGGGCCAGGCCGGGCTCCCAGTGGA 180
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db       4789 AGACCCCCGGGTCCGCCCGGAGCAGCTGCGCTGTCGGGGCCAGGCCGGGCTCCCAGTGGA 4848

Qy        181 TTCGCGGGCACAGACGCCCAGGACCGCGCTCCCCACGTGGCGGAGGGACTGGGGACCCGG 240
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db       4849 TTCGCGGGCACAGACGCCCAGGACCGCGCTCCCCACGTGGCGGAGGGACTGGGGACCCGG 4908

Qy        241 GCACCCGTCCTGCCCCTTCACCTTCCAGCTCCGCCTCCTCCGCGCGGACCCCGCCCCGTC 300
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db       4909 GCACCCGTCCTGCCCCTTCACCTTCCAGCTCCGCCTCCTCCGCGCGGACCCCGCCCCGTC 4968

Qy        301 CCGACCCCTCCCGGGTCCCCGGCCCAGCCCCCTCCGGGCCCTCCCAGCCCCTCCCCTTCC 360
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db       4969 CCGACCCCTCCCGGGTCCCCGGCCCAGCCCCCTCCGGGCCCTCCCAGCCCCTCCCCTTCC 5028

Qy        361 TTTCCGCGGCCCCGCCCTCTCCTCGCGGCGCGAGTTTCAGGCAGCGCTGCGTCCTGCTGC 420
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db       5029 TTTCCGCGGCCCCGCCCTCTCCTCGCGGCGCGAGTTTCAGGCAGCGCTGCGTCCTGCTGC 5088

Qy        421 GCACGTGGGAAGCCCTGGCCCCGGCCACCCCCGCG 455
              |||||||||||||||||||||||||||||||||||
Db       5089 GCACGTGGGAAGCCCTGGCCCCGGCCACCCCCGCG 5123
```

Therefore, it would have been *prima facie* obvious to one having ordinary skill in the art at the time of the invention to combine the teachings of Morin et al., regarding the tumor cell

and tissue specificity of hTERT promoter and its transcriptional regulation in an adenovirus with the teachings of Yu et al. regarding a bicistronic E1A-IRES-E1B cassette expressed by a cell-type specific TRE (transcriptional regulatory element) to be administered intratumorally, to arrive at the claimed vector and methods for killing cancer cells. The sequences of E1A gene (SEQ ID No:1), E1B gene (SEQ ID No:2), IRES sequence (SEQ ID No:3), and hTERT promoter (SEQ ID NO:4) are well known in the art and can be obtained from the sequences disclosed by Stuart et al. (WO 2002/20754), Nemerow et al. (WO 2000/42208), Arya (WO 2000/40741), and Hagen et al. (WO 1999/33998) via PCR cloning taught by Morin et al. (See pages 12-14, Morin et al., 2000).

One having ordinary skill in the art would have been motivated to combine the teachings of Morin et al., Yu et al. because hTERT promoter taught by Morin et al. activate transcription in specifically in tumor cells, and IRES taught by Yu et al. in an intratumorally administered adenoviral vector controlling the expression of E1A and E1B at translational level. The sequences of E1A gene (SEQ ID No:1), E1B gene (SEQ ID No:2), IRES sequence (SEQ ID No:3), and hTERT promoter (SEQ ID NO:4) were well known in the art at the time of filing of instant application by the teachings of Stuart et al. (WO 2002/20754), Nemerow et al. (WO 2000/42208), Arya (WO 2000/40741), and Hagen et al. (WO 1999/33998).

There would have been a reasonable expectation of success given (i) successful identification human TERT promoter and demonstration of hTERT promoter driven reporter gene expression at transcription level by the teachings of Morin et al., (ii) the successful construction and expression from the E1A-IRES-E1B construct, and its translational regulation of E1A and E1B expression exerted by IRES, and intratumoral administration of the adenoviral

construct, by the teachings of Yu et al., and (iii) the sequences of E1A gene (SEQ ID No:1), E1B gene (SEQ ID No:2), IRES sequence (SEQ ID No:3), and hTERT promoter (SEQ ID NO:4) obtainable from the sequences disclosed by Stuart et al. (WO 2002/20754), Nemerow et al. (WO 2000/42208), Arya (WO 2000/40741), and Hagen et al. (WO 1999/33998) via PCR cloning taught by Morin et al. (See pages 12-14, Morin et al., 2000).

Thus, the claimed invention as a whole was clearly *prima facie* obvious.

Conclusion

9. No claim is allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 CFR 1.48(b) if one or more of the

currently named inventors is no longer an inventor of at least one claim remaining in the application. Any amendment of inventorship must be accompanied by a request under 37 CFR 1.48(b) and by the fee required under 37 CFR 1.17(i).

Any inquiry concerning this communication from the examiner should be directed to Wu-Cheng Winston Shen whose telephone number is (571) 272-3157 and Fax number is 571-273-3157. The examiner can normally be reached on Monday through Friday from 8:00 AM to 4:30 PM. If attempts to reach the examiner by telephone are unsuccessful, the supervisory patent examiner, Peter Paras, Jr. can be reached on (571) 272-4517. The fax number for TC 1600 is (571) 273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Wu-Cheng Winston Shen/
Patent Examiner
Art Unit 1632